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Regional gray matter volume and structural network strength in somatic vs. non-somatic delusional disorders

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Short title: Abnormal brain structure in delusional disorders

Abstract

Background: Monothematic delusional disorders are characterized by a single tenacious belief. They provide a great opportunity to study underlying brain structures in the absence of confounding symptoms that accompany delusions in schizophrenia. Delusional beliefs include persecution, jealousy or somatic delusions including infestation. It is unclear whether specific delusional content is associated with distinct neural substrates.

Methods: We used magnetic resonance imaging in patients presenting with somatic vs. non-somatic delusional disorders. Patients with delusional infestation (DI, n=18), and individuals with non-somatic delusional disorders (n=19) were included, together with healthy volunteers (n=20). Uni- and multivariate techniques for structural data analysis were applied to provide a comprehensive characterization of abnormal brain volume at both the regional and neural network level.

Results: Patients with DI showed lower gray matter volume in thalamic, striatal (putamen), insular and medial prefrontal brain regions in contrast non-somatic delusional disorders and healthy controls. Importantly, these differences were consistently detected at regional and structural network level. Compared to healthy controls, patients with delusional disorders other than DI showed lower gray matter volume in temporal cortical regions.

Conclusion: The data support the notion of dysfunctional somatosensory and peripersonal networks that could mediate somatic delusions in patients with DI in contrast to delusional disorders without somatic content. The data also suggest putative content-specific neural signatures in delusional disorders and in delusion formation per se.

Key words: delusional disorders; somatic delusions; MRI, voxel-based morphometry; source-based morphometry; peripersonal space

1. Introduction

Delusional disorders are psychotic disorders characterized by fixed beliefs as a single symptom, sometimes accompanied by hallucinations related to the delusional theme. Therefore, they can be considered as model diseases for single-symptom-based neuroscientific research in psychotic disorders (Corlett et al., 2010). However, delusional disorders are little investigated in neuroscience because patients with these disorders usually fail to consent or adhere to any study protocol (Ahmed and Bewley, 2013; Skelton et al., 2015). Tenacious beliefs in delusional disorders are related to persecution, jealousy, grandiosity, love, nihilism, and misidentification of self and others as well as somatic delusions (delusional disorder somatic type).

A prominent form of delusional disorder somatic type is delusional infestation (DI), also known as delusional parasitosis or Ekbom syndrome (Freudenmann and Lepping, 2009). Patients with DI have the fixed belief that small living or (much rarer) inanimate pathogens such as insects or worms infest their body. They also "feel" them crawling, stinging, biting on the skin or elsewhere in the body, although there is no medical evidence of their presence (Freudenmann and Lepping, 2009; Hylwa et al., 2011). The clinical features of DI often show an overlap between abnormal beliefs (somatic delusions) and abnormal perceptions (Baker et al., 1995). This has been highlighted in the DSM-5 diagnostic criteria for delusional disorder (DSM-5: 297.1), where symptoms of DI are used to illustrate characteristic presence of delusions and hallucinations that mirror these delusions in this group of psychotic disorders ("the sensation of being infested with insects associated with delusions of infestation"). Formerly, DI has been seen rather a disorder of perception ("chronic tactile hallucinosis" according to Bers and Conrad, 1954) or an "organic hallucinosis" (ICD-10). Today, it is mostly referred to as a disorder of thought and reasoning (Trabert, 1995; Freudenmann and Lepping, 2009; Lepping et al., 2015). DI can occur as a primary monothematic delusional disorder (primary DI) or, more commonly, as a secondary delusion. In secondary DI the delusion arises in the context of another major medical, neurological or

psychiatric disorder that affects brain functioning or it is associated with the use of illicit or prescribed substances, usually with dopaminergic mechanism of action (Huber et al., 2007, Dunn et al., 2007; Beach et al., 2014).

A number of case reports suggested frontal, temporo-parietal, striatal and thalamic brain dysfunction in DI let us propose a hypothetical disease model in 2009 (Huber et al., 2008; Freudenmann and Lepping, 2009). We recently introduced the first structural magnetic resonance imaging (MRI) reports using univariate (i.e. voxel-based morphometry [VBM], and multivariate, i.e. source-based morphometry [SBM]) statistical methods for structural data analyses (Wolf et al., 2013; Wolf et al., 2014). Our findings supported the hypothesis that the delusional belief to be infested with pathogens is likely associated with disrupted prefrontal control over somato-sensory representations.

Here, we report the first transnosologic MRI study investigating gray matter volume (GMV) abnormalities in patients with DI and individuals presenting with non-somatic delusions compared to healthy controls. We specifically aimed at identifying structural brain abnormalities that differ within the broad category of delusional disorders when specified by the delusional content, i.e. somatic vs. non-somatic. Whole-brain univariate VBM and multivariate statistical techniques were employed, complemented by a region-of-interest (ROI) approach, to provide a comprehensive characterization of abnormal brain volume at both the regional and neural network level. We predicted that in contrast to patients with non-somatic delusions and healthy controls, patients with DI will show more pronounced structural deficits in subcortical (dorsal striatum, thalamus) and frontal brain regions reflecting aberrant neuroanatomical pathways underlying somatic delusions, especially within the context of DI.

2. Methods

2.1. Participants

We investigated 38 patients presenting with a delusional disorder according to DSM-5 criteria. All participants were right-handed, as identified by their dominant writing hand. Participants were recruited at the Psychiatric Department of the General Hospital Bruneck/South Tyrol, Italy and contacted by phone with the help of the local electronic hospital information system.

We included 18 patients with a delusional disorder, somatic type (DI-group) and 20 patients with non-somatic delusional disorders (NonDI-group). One NonDI-participant was discarded due to insufficient MRI data quality (see section 2.3 below). The healthy control (HC) group included 20 healthy volunteers. 16 DI-patients and 16 HC were already considered in previous works (Wolf et al., 2013 and 2014). None of the NonDI-patients were considered in previous studies.

The DI-group consisted of 10 females and 8 males with a mean age of 74.3 (standard deviation, SD = 8.9) years. In the DI-group 6 patients was classified as primary DI; 3 cases were associated with other mental disorders (2x major depression, 1x cyclothymia); and 9 cases were classified as secondary to various medical conditions (5x subcortical vascular encephalopathy, 1x severe hearing loss/blindness, 1x hyperthyroidism, 1x Parkinson's disease, 1x iron deficiency). Mean disease duration was 6.6 years (SD = 8.9). All patients received antipsychotic treatment (mean chlorpromazine [CPZ] equivalents = 258.4, SD = 125.0, Woods, 2003).

The NonDI-group that was considered for further analyses included 14 females and 5 males with a mean age of 56.1 (SD = 14.9) years. NonDI-patients presented with the following non-somatic delusional content: persecution only (n=9), mixed persecution/poisoning (n=4), jealousy (n=2, without any association to any substance-use disorder), poverty (n=2), hypochondria (n=2). None of the patients fulfilled diagnostic criteria for an underlying affective disorder. Mean disease duration was 13.3 years (SD = 11.2). Three patients were

unmedicated. Sixteen patients received antipsychotic treatment (mean chlorpromazine [CPZ] equivalents = 171.3, SD = 96.4).

HC included 12 females and 8 males with a mean of 70.4 (SD = 11.9) years. HC were considered if they had no psychiatric or neurological history or severe medical condition. None of the HC had a history of psychotropic drug treatment.

None of the participants had a history of substance-use disorder or met criteria for major neurocognitive disorder. All patients were under treatment with antipsychotics for at least one year prior to the MRI recording.

This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All participants gave written informed consent as approved by the local institutional authority (Health District Bruneck/South Tyrol-Italy).

2.2. Structural neuroimaging and data acquisition

Structural data were acquired in the Department of Radiology at the General Hospital Bruneck, South Tyrol, Italy, using an MRI system at 1.0 Tesla (Philips INTERA, Release 11, Best, The Netherlands). The MRI parameters of the 3D T1 gradient echo recalled (fast field echo, FFE) sequence were as follows: TE = 6.9 ms; TR = 25 ms; FOV = 230 mm [AP], 172 mm [RL]; resolution = 0.9 mm^3; number of slices = 170.

2.3. Data pre-processing

A toolbox for VBM (http://dbm.neuro.uni-jena.de/vbm8/) running within the Statistical Parametric Mapping software package version 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm) was used (Ashburner and Friston, 2000; Xu et al., 2009; Kasparek et al., 2010). Data quality procedures included visual inspection and checking for sample homogeneity which led to the exclusion of one NonDI-participant from subsequent analyses (details on data pre-processing are provided as supplementary material). In brief, each participant's original T1

image was segmented into gray matter (GM) and white matter as well as cerebrospinal fluid. Modulated normalized GM segments were smoothed using an 8 mm Full Width at Half Maximum (FWHM) Gaussian kernel prior to between-group analyses at the 2nd level.

2.4. VBM whole-brain analysis

A full factorial model was used including group as a factor; treating age and gender as nuisance variables. An absolute threshold of 0.1 was used to prevent effects occurring at tissue border regions. A main analysis was conducted including HC, DI-patients and the entire NonDI-patient cohort. To account for potential phenomenological diversity in the NonDI-patient sample a second analysis was performed including HC, DI-patients and a subsample of NonDI-patients, i.e. those presenting with prominent paranoid (persecutory) delusions only (n=13). The effect of group was assessed using an F-contrast ($p<0.001$ uncorrected at the voxel level, $p<0.05$ corrected for spatial extent). Post-hoc t-tests were used to assess differences between the groups at $p<0.001$ (uncorrected at the voxel level, $p<0.05$ corrected for spatial extent). Anatomical regions emerging from the 2nd level analyses were labelled according Talairach Daemon (TD) labels and the Automatic Anatomical Labeling Atlas (AAL) (Tzourio-Mazoyer et al., 2002). The stereotaxic coordinates reported in Table 1 were derived from all anatomically distinct regions within in a given cluster surviving the chosen significance threshold. All coordinates are reported in Montreal Neurological Institute (MNI) space. To facilitate comparisons with recent neuroimaging research in non-somatic delusional disorders (Vicens et al., 2016), whole-brain 2nd-level analyses were recalculated using unmodulated segments. For this purpose, we repeated the VBM segmentation to obtain unmodulated normalized data. Using these data, again, a full factorial model was employed where age, gender and total intracranial volume were used as nuisance variables. A significance threshold of $p<0.001$ (uncorrected at the voxel level, $p<0.05$ corrected for spatial extent) was used.

2.5 ROI analysis

In addition to whole-brain data we were also interested in region-wise comparisons between the groups. Since we were primarily interested in the neurobiology underlying DI, we performed ROI-based analyses using a distinct set of subcortical and cortical regions whose contributions to tactile/sensory processing and control is well-known. For this purpose we first entered all GMV images into a one sample t-test model adjusted for age and gender and restricted these analyses to the following set of brain areas, as defined by the AAL atlas: thalamus, bilateral putamen, insula, post-central cortex, middle frontal cortex and anterior cingulate cortex. These ROIs were chosen based on the neurobiological model proposed by us in 2009 and subsequent studies (Freudenmann and Lepping, 2009; Wolf et al., 2013). Subsequently we extracted cluster-wise mean GMV parameter estimates representing the extent of regional volume for each individual. These analyses were performed offline using the Statistical software package (Version 10) using an ANOVA model. A nominal $p<0.05$ was defined, FDR-corrected for multiple comparisons (Benjamini et al., 2001). Fisher's LSD tests were used post-hoc ($p<0.05$).

2.6 Source-based morphometry

We used SBM to investigate the strength of structural networks in between the patient groups as well as between patients and controls (detailed information on SBM is presented as supplementary material). Using individual GMV segments (see section 2.3) a spatial independent component analysis (ICA) was computed. We used the SBM algorithm as implemented in the "Group ICA for f-MRI Toolbox" [GIFT; http://mialab.mrn.org/software/gift] (Xu et al. 2009). Nine independent components were identified, as estimated by minimal description length (MDL) criteria (Li et al., 2007). To increase the stability of the estimated components, we used the Icasso algorithm and repeated the ICA estimation 50 times with bootstrapping and permutation (Himberg et al., 2004). Using ICA, each GMV image was converted into a one-dimensional vector which was arrayed into one 57-row subject/by-segment data matrix. This matrix was decomposed into one mixing and one source matrix. Between-group comparisons were performed using mixing matrix indices. Component

selection and post-hoc between-group comparisons were based on ANOVA models on every column of the mixing matrices. The ANOVA models included a group factor representing HC, DI-patients and NonDI-patients. Analyses were performed offline using the Statistical software package (Version 10). A nominal $p<0.05$, was defined, FDR-corrected for multiple comparisons. Fisher's LSD tests were used post-hoc ($p<0.05$). For component visualization the source matrix was reshaped back to a three-dimensional image, scaled to unit standard deviations (Z maps) and threshold at $Z>2.5$. Maps of interest were overlaid onto a MNI normalized anatomical template. Anatomical denominations and stereotaxic coordinates were obtained from clusters above a threshold of $Z=2.5$ by linking the SBM output to the TD data base (www.talairach.org/daemon.html).

3. Results and statistical analyses

3.1 Demographic data

The patient groups did not significantly differ from each other with respect to gender ($p=0.10$), but DI-patients were older than NonDI-patients ($p = 0.000$). HC and DI-patients did not significantly differ in age ($p = 0.23$) and gender ($p = 0.56$). NonDI-patients were significantly younger than HC ($p = 0.002$) but they did not significantly differ from HC with respect to gender ($p = 0.23$). Disease duration in DI-patients was shorter compared to the NonDI-group ($p = 0.026$). The patient groups differed in terms of CPZ equivalents ($p = 0.014$), with lower mean CPZ equivalents in the DI group compared to NonDI.

3.2 Whole brain VBM analysis

A group effect was found in bilateral parahippocampal, lateral temporal and fusiform cortices, left insula and anterior cingulate cortex (see Figure 1-supplement and Table 1-supplement for detailed stereotaxic coordinates and Z-scores).

These effects were driven by lower GMV in DI-patients compared to HC: in post-hoc comparisons, lower GMV in patients with DI was found in medial and lateral prefrontal areas, medial and lateral regions of the temporal lobe (including the hippocampus and parahippocampus), bilateral fusiform cortices, subcallosal and anterior cingulate cortices, bilateral insula, left putamen, left thalamus and left cerebellum (see Figure 1 and Table 1 for detailed stereotaxic coordinates and Z-scores). In DI-patients, there were no regions showing significantly higher GMV compared to HC.

Compared to HC, patients with delusions *other than DI* (NonDI-group) showed lower GMV in the left inferior temporal cortex (x=-42, y=-1, z=-39, Z=4.98, k=1328) and the right fusiform cortex (x=26, y=-69, z=-8, Z=4.98, k=417) (see Figure 1). In these patients, there were no regions showing significantly higher GMV compared to HC. No significant differences emerged when DI-patients were contrasted to NonDI-patients. When analyses were repeated using a subgroup of patients with prominent paranoid (persecutory) delusions only, a similar pattern of GMV volume loss was obtained. Findings in the DI-patient group compared to HC remained largely unchanged. In the NonDI-patients subgroup with prominent paranoid (persecutory) delusions lower GMV compared to HC was found in the left inferior temporal cortex (x=-42, y=-1, z=-39, Z=4.33, k=481) (see Figure 1). None of the patient groups showed higher GMV compared to HC. The patient groups did not significantly differ from each other.

Using unmodulated segments, findings in the DI-group vs. HC and vs. NonDI-patients remained largely unchanged ($p<0.001$, uncorrected). Compared to HC, NonDI-patients showed lower GMV in the left insula (x=-45, y=-13, z=-7, Z=4.13, k=481), the left inferior temporal cortex (x=-41, y=0, z=-39, Z=3.85, k=260), the right fusiform cortex (x=23, y=-42, z=-11, Z=3.75, k=292), in a cluster comprising the right superior temporal gyrus and the parahippocampal gyrus (x=33, y=18, z=-33, Z=3.72 and x=33, y=11, z=-32, Z=3.60, k=421) and in the right inferior temporal gyrus (x=54, y=-35, z=-27, Z=3.70, k=273) (see Figure 3-supplement).

3.3 ROI analysis

Except for the bilateral middle frontal cortex a significant group effect was found for each of the remaining ROIs. Post-hoc tests revealed that patients with DI had significantly lower volumes compared to HC and patients with other delusions (NonDI-group) in the bilateral putamen, thalamus, insula and the anterior cingulate cortex. For the bilateral postcentral cortex post-hoc tests revealed significantly lower GMV in patients with DI compared to NonDI-patients. In all post-hoc tests, there were no significant differences between HC and NonDI-patients (detailed statistics and GMV plots showing regional extent of GMV across the groups are available on request).

3.4 Network SBM analysis

Nine components were estimated using MDL criteria. Three of these components showed a significant effect of group ($p<0.05$, FDR-corrected). Two components were chosen for further post-hoc analyses (see Figure 2 and Table 2 for detailed anatomical labels, coordinates and Z-scores); one component clearly signalled head movement artefacts and was thus discarded (see Figure 2-supplement). The first significant ($F(2, 54)=3,7671$, $p=.0294$) component of interest (COI1, “striatal network”) displayed a pattern of predominantly bilateral striatal and thalamic regions together with areas of the frontal cortex. Post-hoc tests revealed that patients with DI had lower GMV than HC ($p=0.013$) and patients with other delusions (NonDI-group) ($p=0.036$). There were no differences between HC and the NonDI-group ($p=0.689$). The second significant ($F(2, 54)=5,3625$, $p=.0075$) component of interest (COI2, “frontotemporal network”) included predominantly the bilateral insula, medial and lateral temporal areas and anterior cortical midline regions. Post-hoc tests revealed that patients with DI had lower GMV than HC ($p=0.026$) and patients with delusions other than DI ($p=0.002$). There were no differences between HC and patients from the NonDI-group ($p=0.348$).

4. Discussion

This structural MRI study investigated brain structure of patients with somatic and non-somatic delusional disorders at the regional level and at the level of structural network expression HC. Our results provide first evidence that patients with somatic delusions, i.e. DI, differ from patients with non-somatic delusional disorders and HC. More specific, DI patients exhibited a pattern of lower GMV in fronto-thalamo-striatal and frontotemporal regions. In contrast to our previous studies, our findings indicate that the brain changes observed in DI are more pronounced in this form of delusional disorder, in contrast to delusions with other monothematic content. Importantly, the volume differences found in the patient groups were not restricted to the regional level, as shown by whole-brain VBM and pre-defined ROI analyses, the latter providing clear differences between individuals with and without somatic delusions. At the level of structural network expression (SBM) two networks were identified as abnormal in patients with DI in contrast to the patients with other delusional disorders and HC. In both components of interest, striatal and frontotemporal, patients with DI showed significant lower GMV compared to both patients with non-somatic delusions and HC.

The findings share some key features with those seen in the unfortunately small number of studies imaging patients with delusional disorders in general (Su et al., 2001; Kunert et al., 2007; Vicens et al., 2016). So far, brain correlates of delusions are studied systematically mainly in patients with schizophrenia (Knobel et al., 2008). Interestingly, imaging studies in somatic delusions in patients with schizophrenia found GMV-abnormalities (frontal, insular, thalamus) similar to the present study in DI (Cascella et al., 2001; Spalletta et al., 2013). Patients with non-psychotic chronic skin manipulations, behaviours typically seen in DI (itch-scratch-cycle), also showed brain abnormalities in thalamo-striatal and orbitofrontal regions (Schneider et al., 2008; Mochizuki et al., 2009). This may suggest that common neural pathways could underlie the expression of somatosensory phenomena, probably regardless of nosological considerations.

We provide further evidence for pathology in the dorsal, somatic *striatum (putamen) in* DI. Importantly, the abnormal striatal volume in the DI-patients was confirmed (in contrast to the NonDI-patients and HC) by all our performed distinct analyses (whole-brain VBM, ROI-analysis and SBM), suggesting a robust finding in DI. This supports the notion that the basal ganglia, particularly the dorsal striatum (putamen), are involved in various perception processes such as in visuo-tactile perception and sensory predictions (Ladavas et al., 1998; Yoo et al., 2003; Colder, 2015). The putamen is known as an essential node of the so called "Peripersonal Space Network" relevant for the neural integration of visual with tactile information (visuo-tactile perception) near, but outside the body (Graziano and Gross, 1993, Gentile et al., 2011; Brozzoli et al., 2014). This network is well researched with neuroimaging in human beings and includes frontal, parietal, insular and subcortical (putamen) brain areas where visual and tactile signals converge (Brozzoli et al., 2012; Di Pellegrino and Ladavas, 2015). The so-called "Peripersonal Space Network" is thought to play a fundamental role in the representation of the space in the immediate vicinity of the body (10-20 cm), permitting the construction of a special cerebral encoding of the space that lies in the boundary zone between objects near the body and the body itself (Di Pellegrino and Ladavas, 2015; de Vignemont and Iannetti, 2015). Thus, DI may underlie a specific malfunction of the so-called "Peripersonal Space Network".

In the present DI sample, the bilateral postcentral gyrus showed lower GMV in the ROI-based analyses only. This was unexpected given that DI patients usually suffer from intense sensations in their skin or body. However, converging evidence suggests that perception of touch in humans does not only require the postcentral gyrus and parietal operculum but also involves the insular cortex and putamen together with prefrontal structures as well as superior temporal and limbic structures (Nagy et al., 2006; Auksztulewicz et al., 2012 Preusser et al., 2015). We also found evidence for structural brain changes in insular cortex, a brain region known to mediate feelings of disgust and as a potential source of interoceptive predictions (Wicker et al., 2003; Craig, 2003; Paulus and Stein, 2009). Similarly, a recent functional MRI study in DI patients found changes in neural activity not only in frontal but also

insular and temporal cortices next to limbic structures, such as the amygdala (Eccles et al,. 2015). Structural brain changes in these regions in people with delusions would be consistent with disturbed interaction between top-down expectation and bottom-up input that may cause prediction errors and delusional beliefs (Schmack et al., 2013; Barrett and Simons, 2015; Pia et al., 2015). However, disturbances in the primary somatosensory cortex and right frontal cortex would be more consistent with the two-factor theory of monothematic delusions (Davies et al., 2001; Coltheart, 2010).

The frontostriatal abnormalities support the notion that somatic delusions could essentially originate prefrontal failure to optimize visuo-tactile uncertainty, leading to an impaired judgment with abnormal delusional beliefs and errors of probabilistic reasoning. In this model, dysfunctional processing in the dorsal striato-subcortical loop could explain abnormal visuo-tactile perceptions (hallucinations) presumably mediated by the damaged putamen (dorsal “somatic” striatum). This may support that delusions originate from a neural network failure between top-down and bottom-up processing as mismatches between expectations and experience (aberrant prediction errors) (Fletcher and Firth, 2009; Ding and Gold, 2013; Colder, 2015; Adams et al., 2016; Chanes and Barrett, 2016). Yet it is very challenging to distinguish two-factor and predictive coding explanations of delusions on the basis of structural data alone, as they make different predictions about information processing rather than brain structure (Corlett et al., 2007 and 2010; Corlett 2015).

Potential limitations of this study include the modest sample sizes and the use of psychotropic medication in the patient samples. Nevertheless, given the difficulties to motivate patients with monothematic delusions (and especially those with DI) to participate in a study, we consider the present sample sizes as relatively large compared with the few other currently available studies investigating the neural underpinnings of delusional disorders. Similarly, the presence of an antipsychotic agent in these patients reflects common clinical practice. We are not aware of any study so far presenting data from antipsychotic-naïve DI-patients, as much as we are not aware of studies which investigated antipsychotic-naïve patients with delusional disorders other than DI. Antipsychotic treatment

can have an impact on brain structure. Yet the differences in GMV change and structural network strength, as observed in DI vs. nonDI, cannot be solely attributed to antipsychotic treatment, since CPZ equivalents differed between the patient groups, with DI-patients being treated with lower dosages of antipsychotics compared to NonDI. Age and disease duration need to be considered as potentially relevant variables as well, since the NonDI-group was significantly younger compared to both DI-patients and HC, and since NonDI-patients presented with longer disease duration. However, we included age as nuisance variable in all analyses, and it is difficult to assign more pronounced gray matter volume loss to shorter disease duration, as observed in the DI-group. Also, the DI group is etiologically more heterogeneous than the NonDI-group, as it includes patients with affective disorders and various medical conditions. Nevertheless, we have previously shown that at least in terms of structural network strength, frontostriatal and insular dysfunction in DI-patients is independent of etiological considerations Wolf et al., 2014). In the context of our study, we emphasize the clinical phenotype and its potential neural substrates and not a specific (putative) etiology, keeping in mind that such approaches could potentially hamper transnosological observations. Eventually, we also acknowledge that any hypotheses regarding functional mechanisms are speculative at this stage because we are inferring from structural data. Functional and structural abnormalities in patients with delusional disorders can co-occur (Vicens et al., 2016). It is, however, unclear whether structural deficits drive functional abnormalities or whether two distinct levels of neural dysfunction (i.e. structure and function) differentially contribute to symptom expression. These questions are clearly of outstanding interest, and future research in delusional disorders clearly has to consider these distinct levels of neuropathology and their interrelationships.

5. Conclusion

Keeping this study's limitations in mind, we provide a comprehensive analysis of brain structure in patients with somatic and non-somatic delusional disorders. Our findings support the notion of dysfunctional sensorimotor and peripersonal neural pathways that could mediate somatic delusions in patients with DI in contrast to non-somatic delusional content. The data suggest putative content-specific neural signatures in delusional disorders and in delusion formation per se. Future multimodal neuroimaging studies, i.e. combined functional and structural MRI protocols, are desirable address this specific hypothesis, and to establish robust links between specific symptom expression, i.e. delusional content, and its neural underpinnings.

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7. Figure legends

Figure 1. **Top**: Regions showing lower gray matter volume (GMV) in patients with delusional infestation (DI) compared to healthy controls. Shown are results of 2nd level between-group analyses, $p<0.05$ corrected for spatial extent (see also Table 1 for detailed stereotaxic coordinates and Z-scores). The statistical maps are rendered onto the anatomical templates implemented in SPM8. The color bar represents T-values. **Bottom**: Regions showing lower gray matter volume (GMV) in patients with delusional disorders other than DI (NonDI-group) compared to healthy controls. Left: Results obtained across the entire patient sample. Right: Results obtained using a subset of patients (n=13) presenting with prominent paranoid (persecutory) delusions. Shown are results of 2nd level between-group analyses, $p<0.05$ corrected for spatial extent (see also Table 1 for detailed stereotaxic coordinates and Z-scores). The statistical maps are rendered onto the anatomical templates implemented in SPM8. The color bar represents T-values.

Figure 2. Structural networks exhibiting differences in patients with delusional infestation (DI) compared to healthy controls and compared to patients with delusional disorders other than DI (NonDI-group) (see also Table 2 for detailed anatomical labels, coordinates and Z-scores). Shown are the two GMV components which showed a significant group effect as a result of an ANOVA, $p<0.05$, FDR-corrected.

* indicates significant between group differences as revealed by post-hoc Fisher's LSD tests. "n.s." indicates non-significant findings. For visualization purposes the components were thresholded at $Z>1.0$ and rendered onto the anatomical template implemented in GIFT. The color bar indicates the Z-value. L: left, R: right.